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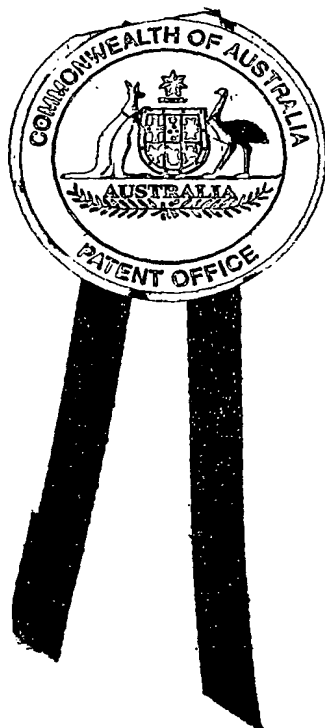
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METHOD OF PREDICTING FUNCTIONAL OUTCOME OF A STROKE USING EEG MEASURES

This invention relates to a method of predicting the evolution and functional outcome of a stroke or similar ischaemic infarction, using EEG measures acquired in the acute phase of a stroke, i.e. obtained shortly after the onset of stroke symptoms.

BACKGROUND ART

Typically, a person suffers an ischaemic infarction or stroke when a blood vessel is blocked, causing cerebral nervous tissue to be deprived of oxygen. In the initial few hours after a stroke, there is usually a significantly reduced blood supply to a region of nervous tissue due to a blocked or nearly-blocked blood vessel which would otherwise supply oxygen to that tissue. The nervous tissue deprived of adequate blood supply does not necessarily die immediately. It can often die over the next 18 hours or so. The prediction of the final size of the stroke, i.e. the final volume of dead tissue is very difficult.

If the stroke evolution is known, the patient can receive appropriate treatment. The efficacy of drugs can also be evaluated. One of the major challenges in acute stroke research and treatment is to accurately identify, predict and monitor the progression of stroke evolution.

Known methods of stroke evaluation generally rely on the use of subjective measures such as operator defined regions of interest on diffusion and perfusion maps to enable prediction of infarct size. However, these methods are time consuming to implement and require highly skilled practitioners. Further, there is a limited time window of opportunity for the administration of thrombolytic or neuroprotective therapy.

The principal EEG indices of stroke and other ischaemic brain insults are well documented. The most common finding is a shift to a preponderance of high-voltage, slow delta oscillations, largely localised to EEG acquired from electrode sites overlying the ischaemic area. This increase in delta power (voltage squared) may be accompanied by a

concomitant increase in theta power, and/or by a decrease in alpha power (particularly when the lesion encompasses occipital or parietal areas).

Quantitative EEG (QEEG) techniques include the computation of power and associated scalp topographic maps, for given frequency bands. Such techniques have been used during the past three decades to illustrate, diagnose, and investigate brain pathophysiology following stroke (e.g., Cohen et al., 1976; Nagata et al., 1982; Nuwer et al., 1987; Murri et al., 1998; Luu et al., 2001; Fernandez-Bouzas et al., 2002), and the efficacy of QEEG in this context has been well-demonstrated. For example, QEEG topographic maps have been shown to indicate pathophysiological foci before they are detectable in computed tomography (CT) scans (Nagata et al., 1982), and such foci have been demonstrated to reliably correlate with the location of the lesion as indicated by CT and MRI (Murri et al., 1998; Nuwer et al., 1997; Fernandez-Bouzas et al., 2002). In addition, it has recently been reported that QEEG variables, derived from data acquired within 72 hours of the stroke, can be employed to predict subsequent clinical outcomes following ischaemic stroke and further, that these variables possess higher prognostic value than the Canadian Neurological Scale in this context (Cuspineda et al., 2003).

Previous investigations have typically collected a maximum of twenty minutes of EEG data at some point within the first 24 to 36 hours (e.g. Murri et al., 1998; Luu et al., 2001) or within the first 3 to 4 days (e.g., Fernandez-Bouzas et al., 2002; Cuspineda et al., 2003), post-stroke. However, QEEG data has not been employed to systematically index brain pathophysiology over the course of several hours, in the acute post-stroke phase.

Neuroimaging techniques, based on the use of diffusion and perfusion weighted MRI have been shown to be extremely useful for the identification of ischemic tissue and more importantly, for predicting functional outcome. International patent application no. PCT/AU02/00256 describes a method for predicting infarct evolution using magnetic resonance imaging (MRI) and image processing.

A number of measures derived from magnetic resonance imaging (MRI) data have previously been shown to correlate with functional outcome. Expansion of the ischemic territory delineated on diffusion and

perfusion weighted images acquired in the acute phase of stroke has correlated with clinical outcome measured using the National Institute of Health Stroke Scale scores or Canadian Neurological Scale.¹⁻⁴ It has also been demonstrated that these MRI measures can be mathematically modelled to predict final lesion volume.^{5,6} However due to a host of clinical, logistical and economic issues, MRI is not particularly practicable for continuous systematic investigations of the development of acute post-stroke brain pathophysiology over the course of hours.

SUMMARY OF THE INVENTION

This invention provides a method of predicting neurological developments resulting from a stroke or like cerebral ischaemia, comprising the steps of acquiring EEG measures from a patient in an acute phase of the stroke, processing the acquired data to obtain a power spectrum in the delta band, and interpreting the delta power metrics to predict subsequent and/or eventual clinical and/or functional neurological outcome in the patient from the stroke.

Typically, the power spectrum is obtained by a Fast Fourier Transform of artefact-free portions of the acquired EEG data. Preferably, the EEG data is acquired within 12 to 15 hours, and commencing within 7 hours, of onset of symptoms of stroke in the patient. The EEG data can suitably be acquired from electrodes distributed evenly across the scalp of the patient (and particularly from electrodes placed on regions of the scalp overlying the stroke).

A preferred embodiment comprises the following steps:

1. Multi-channel EEG data is acquired within the acute phase of stroke using scalp electrodes, and artifact free periods of high quality data are selected.
2. The artifact free EEG data is bandpass filtered, separated into contiguous segments, and frequency band power is calculated for each electrode at a series of frequency points over a frequency range using the Fast Fourier Transform.
3. An "average scalp power spectrum" is computed by calculating the mean power (at each frequency point) across all scalp electrodes. The frequency at which peak power occurs is determined in each patient's average scalp power spectrum and is verified in power spectra from several electrodes overlying

the location of the stroke in the brain. This frequency is in the *delta* band (0.5-4 Hz), but varies from patient to patient. The power associated with this peak frequency is determined for each portion of artifact-free EEG data.

5. This delta power metric in data from one time-point is then subtracted from the same metric obtained at the next such time-point, and this difference score is divided by the time that had elapsed between these two time-points in order to calculate the slope of a line constituting the cross-temporal change in delta power. The resulting slope value is then converted to a quotient of the original delta power metric.

Reduction in delta power as recorded on EEG can provide an indication of subsequent clinical improvement in stroke patients over the following hours and up to 30days.

More sensitive measures of EEG coherence (both linear and non-linear) can be used to predict clinical and functional outcomes from stroke.

A combination of EEG delta changes, combined with MRI data obtained from the same patient at the same time, will improve prediction of stroke outcome.

The method of this invention has several advantages. First, the derivatives of data acquired from acute stroke patients allow prediction of the effects and efficacy of putative neuroprotective and thrombolytic agents, thereby enhancing the efficacy of the clinical management of acute stroke patients.

Given the unparalleled millisecond-scale temporal resolution of EEG in the monitoring of dynamic brain function, determination of the QEEG correlates of, for example, substantial recovery following re-perfusion in the acute post-stroke period, significantly enhances acute treatment decisions relating to the administration of appropriate pharmaceutical interventions and assists in assessing the efficacy of such interventions.

Furthermore, the identification of cross-temporal QEEG correlates of brain pathophysiology in the acute post-stroke period can be employed to generate an electrophysiological predictive model of stroke evolution and functional outcome.

Secondly, EEG data can be continuously collected from patients whilst in their hospital beds, and this is relatively very inexpensive to acquire

due to low relative cost of EEG equipment.

These factors place the methodology of this invention in an optimal position to monitor acute post-stroke brain pathophysiology, and to yield indices which can be employed to effectively predict stroke evolution and to acutely assess the efficacy of pharmaceutical interventions.

In order that the invention may be more fully understood and put into practice, an example thereof will now be described.

DESCRIPTION OF AN EXAMPLE OF INVENTION

To demonstrate that QEEG measures acquired in the acute phase of stroke can be used to predict stroke evolution and functional outcome (particularly compared to existing established techniques utilising diffusion and perfusion weighted MRI), serial QEEG measures were recorded from a sample of acute stroke patients and correlated with functional outcome. In addition, the relationship between these measures and the expansion of the diffusion MRI lesion into the surrounding penumbral region, delineated by the diffusion – perfusion mismatch territory, was also investigated.

Clinical Data from Stroke patients

The National Institutes of Health Stroke Scale Score (NIHSSS) was used to evaluate neurological impairment from stroke. The scale is an 11-item, clinical evaluation instrument widely used in clinical trials and practice, the reliability and validity of which is widely documented. The scale was administered on admission and at 24 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours, and 30 ± 2 days, post-stroke.

EEG data acquisition and analysis

Following the first MRI scanning session, patients were taken to their beds in a hospital ward. An elastic cap (Quik-Cap, Neuromedical Supplies) in which were embedded 62 sintered Ag/AgCl scalp electrodes, was fitted to each patient's head. Electrode locations corresponded to the following sites of the International 10-20 system (Jasper, 1958): FPz, FP1, FP2, AF3, AF4, AF7, AF8, Fz, F1, F2, F3, F4, F5, F6, F7, F8, FCz, FC1, FC2, FC3, FC4, FC5, FC6, FT7, FT8, Cz, C1, C2, C3, C4, C5, C6, T7, T8, CPz, CP1, CP2,

CP3, CP4, CP5, CP6, TP7, TP8, Pz, P1, P2, P3, P4, P5, P6, P7, P8, POz, PO3, PO4, PO5, PO6, PO7, PO8, Oz, O1, O2. Vertical eye movements and blinks were monitored via two electrodes, one placed on the supraorbital ridge of, and one below, the left eye. Horizontal eye movements were monitored via two electrodes, one on the outer canthus of each eye. At acquisition, all electrodes' signals were referenced to a linked pair of electrodes, one positioned on each mastoid process. All electrodes were filled with conducting gel prior to data acquisition. Electrode impedances were predominantly 10-20 k Ω or less. EEG data was filtered (bandpass; 0.01-100 Hz) online and digitised at a sampling rate of 500 Hz.

Recordings were made using a Neuroscan SynAmps 64 channel digital EEG amplification and acquisition system. EEG was acquired continuously from the earliest practicable time post-MRI scan (approximately 7 ± 2 hours post-stroke) until 15 ± 2 hours post-stroke. At least several minutes of "high-quality", artefact-free EEG data was acquired within both the first and last hours of recording, during which times the patient was awake but resting quietly and still with eyes closed, with zero or minimal ambient noise and other activity in the room or immediate vicinity. Where practicable (when EEG data was not acquired throughout the entire course of the night), several minutes of EEG data were also generally acquired under such optimal conditions at a time between one and three hours after the first high-quality EEG time-point. In addition, between 20 and 30 minutes of EEG data were acquired under those conditions at 24 ± 2 hours, 48 ± 2 hours, 72 ± 2 hours, and 30 ± 2 days, post-stroke.

Although EEG data was acquired continuously between approximately 7 ± 2 hours and 15 ± 2 hours post-stroke, it was predominantly each of the segments of high-quality data that were submitted to the following analyses: Three minutes of continuous artefact-free EEG data was filtered (bandpass; 0.2-40 Hz; 24 dB/octave), separated into contiguous segments each comprising 2048 data points, and EEG bandpower (representing voltage amplitude squared) was calculated for each electrode and at each 0.25 Hz point (over the range 0.5-40 Hz), using the Fast Fourier Transform. In data

from each time-point, an "average scalp power spectrum" was computed by calculating the mean power (at each frequency point) across all 62 scalp electrodes. The frequency at which peak power occurred, was determined in each patient's average scalp power spectrum. This frequency was always in the *delta* band (0.5–4 Hz), but varied between 1 and 1.75 Hz from patient to patient. The power associated with this peak frequency was determined for each portion of high-quality EEG data. This delta power metric in data from the first high-quality EEG data time-point was subtracted from the same metric obtained at the second such time-point, and this difference score was then divided by the time (in hours) that had elapsed between these two time-points in order to calculate the slope of a line constituting the cross-temporal change in delta power. The elapsed time varied between one and nine hours (with higher values occurring for cases wherein data was recorded throughout the night). The resulting slope value was then converted to a quotient of the original delta power metric, and this quotient was subsequently correlated with patients' functional outcomes as indexed by a function of observed changes in NIHSS scores over time. That function was also computed as the change between time points one and two, divided by the elapsed time between these, and then by the original NIHSS score.

It was found that there is a strong relationship between reduction in delta power as recorded on EEG and subsequent clinical improvement over the following hours and up to 30days in stroke patients as measured using clinical rating scales. As shown in Fig 4, there is a strong correlation between acute changes in Delta power (in the average scalp power spectrum), and functional outcome at 72 hours post-stroke as indexed by the NIHSS. Across the six subjects' data illustrated, Pearson's correlation coefficient is highly significant at $r = 0.94$ (out of a possible maximum of 1).

Thus, changes in delta power can be used to predict likely stroke development. Where drug therapy is applied, the efficacy of such therapy can be evaluated by reference predicted functional outcome.

The predictive approach may use regression, a statistical procedure that regularly follows that of correlation. A "line of best fit" or "regression line" is plotted to the data, using the *Least Squares* criterion. (This

can be computed easily via any one of a number of standard computerised statistical packages). The subsequent change in NIHSS score (termed Y ; be it at 72 hours or 30 days, post-stroke [a different plot and regression line is of course used for each time-point]) can then be predicted on the basis of three variables:

1. The acute change in Delta power metric (termed X);
2. The slope of the regression line (i.e., the change in value on the Y -axis when X changes one unit; termed b); and
3. The intercept of the regression line (i.e., the predicted value of Y when X is zero; termed a).

This is achieved via use of the following regression equation:

$$Y = bX + a$$

Predictive example based upon the six patients' data illustrated in Fig 4:

- Pearson's correlation coefficient, $r = 0.94$
- In this data set, the slope of the regression line, $b = 3.27$; and the intercept, $a = -0.05$
- A stroke patient presents with an initial NIHSSS of 25
- EEG data is recorded from 7 hours to 13 hours post-stroke (with 3 minutes of high-quality, artefact-free data acquired at start and end)
- Initial Delta power at 7 hours (in the average scalp power spectrum) is 82.7, and at 13 hours is 26.5 (units are microvolts squared)
- The slope of the "delta change" line is calculated as -9.37 (i.e. $[26.5 - 82.7]$ divided by 6 [the number of hours elapsed])
- The Delta change metric is calculated as -0.11 (i.e., the Delta slope value, -9.37 , divided by the initial Delta power value of 82.7); this serves as the X -value for the regression equation
- The predicted change in NIHSS score over 72 hours, Y , is calculated using the abovementioned regression equation as -0.42 (i.e., 3.27 multiplied by -9.37 , plus -0.05)
- This NIHSS change represents the NIHSS score at the latter time-point minus the initial such score, and the difference divided by the initial

score. Hence the predicted NIHSS at 72 hours post-stroke would in this case be 14.5

The foregoing describes only one example of the invention, and the invention is not limited thereto. For example, the general methodology of this invention may be applied to other cerebrovascular disorders (such as brain haemorrhages, various forms of hypoxia [disruption of regular oxygen supply to the brain], and severe migraines) which elicit similar EEG outcomes to stroke (e.g., pronounced slowing of the brain's electrical oscillations, leading to high Delta power), as well as coma states, traumatic brain injuries and possibly mild traumatic brain injuries such as concussion. Related analysis & prognostic strategies (which might take into account EEG frequency bands other than Delta) might be applied to other brain disorders such as mild cognitive impairment (a precursor of Alzheimers disease and other dementias) and epilepsy.

Table 1. Patient Demographics, Vascular Territory, Time of MRI scanning and recording of EEG and NIH Stroke scores.

Patient	Age Y/sex	Vascular Territory	Acute Measurement Time (hrs)		NIHSS			NIHSS evolution*
			MRI	EEG	Initial	48 h	30 d	
B260834	83/F	RPCA	3.5	6.0	14	13	5	-0.07
B403212	57/F	LMCA	5.0	6.5	7	3	2	-0.57
B534926 [†]	83/F	RMCA	7.0	8.0	22	23	NA	0.05
B583134	55/M	RICA	3.0	5.0	5	3	2	-0.40
B027915	87/F	RMCA	5.5	7.5	19	15	9	-0.17
B633579	64/M	LMCA	4.5	6.0	4	2	1	-0.60
1143328	85/M	LMCA	5.5	7.0	25	17		-0.32
B536200 ^{††}	67/M	LMCA	4.5	6.0	21	13		-0.38
B515182 [†]		LMCA		6.25	33	NA	NA	

[†] Patient died before 30-day follow up scan, ^{††} Patient received tissue Plasminogen Activator after initial MRI scan and EEG recording, * NIHSS evolution is defined as the difference between the 48 hour and sub 6 hour NIH stroke score divided by the initial score.

Table 2. Acute and follow up MRI and EEG measures

Patient	Lesion Volumes (ml)				Acute DWI Expansion Rate*	EEG Delta Power Change [‡]
	DWI 6 h	MTT 6 h	DWI 15h	T2 30 d		
B260834	5.6	14.8	7.7	4.6	0.14	-0.05
B403212	25.3	188.3	29.8	5.4	0.02	-0.17
B534926 [†]	205.7	424.8	263.9	NA	0.14	0.04
B583134	26.6	50.4	29.5	9.1	0.06	-0.09
B027915	32.8	108.2	46.9	20.9	0.13	-0.04
B633579	11.1	98.1	12.4	5.2	0.01	
1143328						-0.06
B536200 ^{††}	134.5	199.8	143.0	64.3	0.05	-0.43
B515182 [†]						

[†] Patient died before 30-day follow up scan, ^{††} Patient received tissue Plasminogen Activator after initial MRI scan and EEG recording, * Acute DWI expansion rate is defined as the difference between the 15 hour and sub 6 hour diffusion lesion volume divided by the initial sub 6 hour MTT volume. [‡] EEG delta power change is defined as the difference between the 15 hour and initial delta power divided by the time elapsed between EEG recordings. A resulting value for this metric was then derived as a quotient of the original delta power.

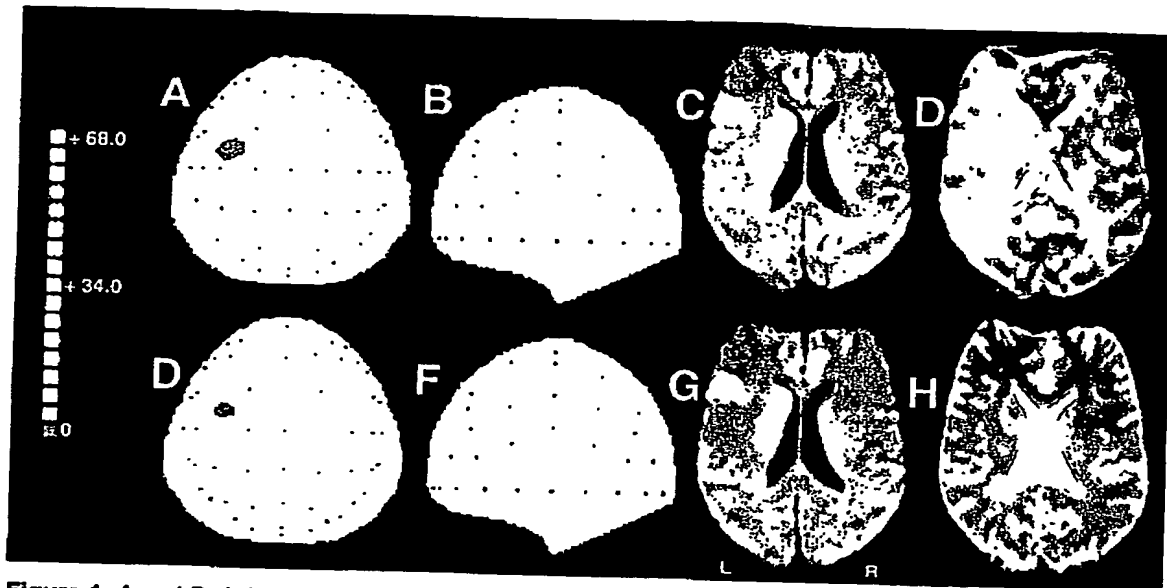


Figure 1: A and B: Axial and sagittal EEG Scalp Topographic Delta Power maps acquired 7 hours after onset of symptoms; C: initial DWI (6 hours after onset of symptoms); D: initial MTT map; E and F Axial and sagittal EEG Scalp Topographic Delta Power maps acquired 13 hours after onset of symptoms; G: 15 hours DWI scan and H: follow-up T2 MRI.

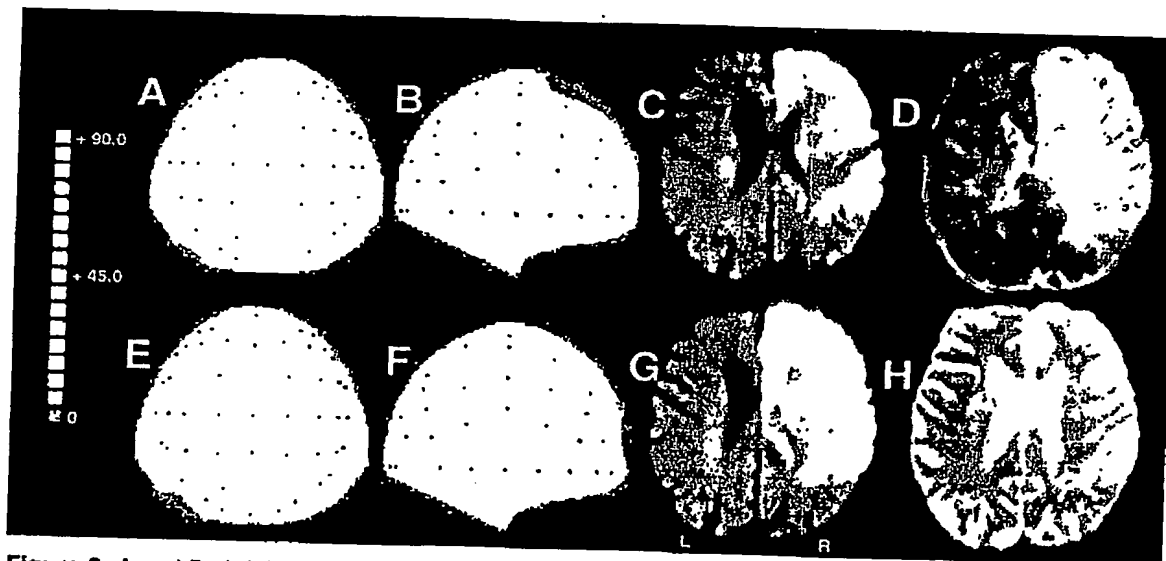


Figure 2: A and B: Axial and sagittal EEG Scalp Topographic Delta Power maps acquired 9 hours after onset of symptoms; C: initial DWI (6 hours after onset of symptoms); D: Initial MTT map; E and F Axial and sagittal EEG Scalp Topographic Delta Power maps acquired 17 hours after onset of symptoms; G: 15 hours DWI scan and H: follow-up T2 MRI.

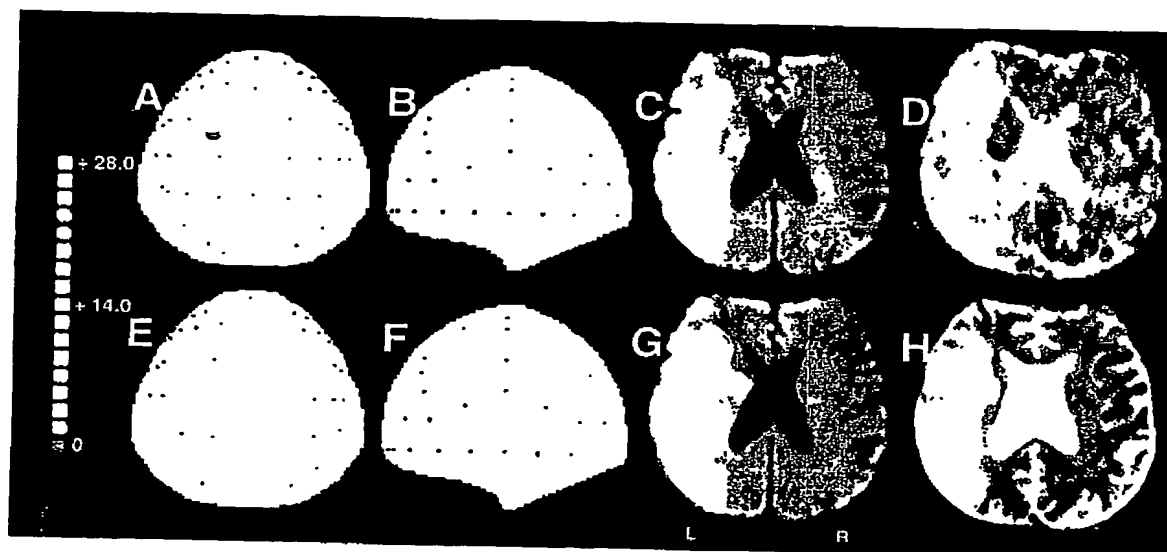


Figure 3: A and B: Axial and sagittal EEG Scalp Topographic Delta Power maps acquired 6 hours after onset of symptoms; C: Initial DWI (4.5 hours after onset of symptoms); D: initial MTT map; E and F Axial and sagittal EEG Scalp Topographic Delta Power maps acquired 12 hours after onset of symptoms; G: 13 hours DWI scan and H: follow-up T2 MRI.

Percentage changes over time: EEG Delta Power (Acute phase, all electrodes) versus NIHSSS (72 hrs post-stroke)

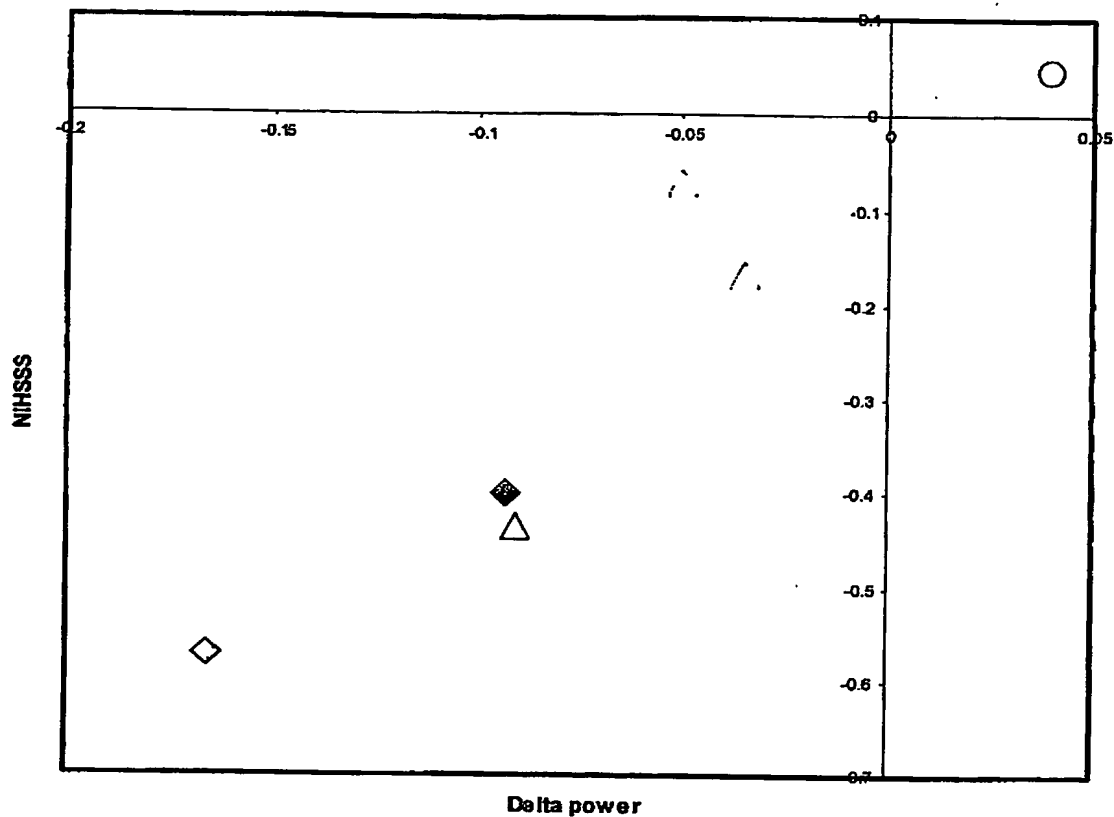


Figure 4

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